DARTMOUTH-HITCHCOCK MEDICAL CENTER

James P. AuBuchon, MD, FCAP, FRCP(Edin)
E. Elizabeth French Professor and Chair of Pathology
Tel: (603)650-8693
Fax: (603)650-4845
JAMES.P.AUBUCHON@HITCHCOCK.ORG

October 21, 2005

Division of Dockets Management (HFM-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20861

Re: Draft Guidance: Collection of Platelets by Automated Methods, September, 2005

Dear Sirs:

Please accept the following comments for consideration related to the draft guidance, "Collection of Platelets by Automated Methods".

Page 6, Donation Frequency: Donation frequencies should be determined by a donor's platelet count and reasonable volume limitations.

1. Given the limits set in this and other guidances and regulations regarding the minimum platelet count of a donor and the maximum plasma volume allowed to be collected per donation and per annum, setting additional limits on the frequency of donation based on the type of platelet collection (i.e., single vs. double vs. triple) is unnecessarily restrictive and not necessary to ensure donor safety. The stated interval of 2 days between donations and no more than two donations in a seven-day period seems reasonable and appropriate. However, since the donor's platelet count must remain above 150,000/μL to retain donation eligibility and since the maximum volume collected at each donation is determined by the donor's weight (at either 500 or 600 mL), imposing more restrictive (i.e., longer) interdonation intervals after double- or triple-unit collection procedures are entirely unnecessary. (Thus, all plateletpheresis donations should be treated similarly, regardless of the number of platelets actually collected.)

2. Similarly, continuing to restrict the number of donations to 24 per year lacks any basis in hematopoietic physiology. My recall is that this limitation was based primarily on concern for leukocyte (especially lymphocyte) loss with generations of apheresis instruments that are now long out of use. No annual maximum should be stated.

Page 7, Medical Coverage: The requirement for a physician to be available within 15 minutes to attend a donor undergoing plateletpheresis is unnecessary and unnecessarily restrictive. The guidance should require (1) the prompt (i.e., within minutes) availability of assistance from a medical practitioner (such as a registered nurse) familiar with the causes and treatments of medical problems associated with apheresis; (2) a similarly rapid availability of telephone contact with a physician trained and knowledgeable in such areas (e.g., a physician associated with the collecting facility); and (3) a validated, viable plan to obtain medical assistance on-site within 15 minutes from either a licensed physician or emergency medical personnel and services.

1. Currently available, microprocessor-controlled apheresis instruments have an extremely high-rate of reliability. Coupled with low extracorporeal volumes and minimized citrate usage, significant donor reactions are rare and are usually readily handled by trained collection personnel. Those reactions requiring additional care could be initially handled well by a trained nursing observer reporting to a trained physician who could then direct additional interventions as needed.

2. In the very rare case where further medical intervention were required, transport to an emergency medical facility would probably be necessary. The prior establishment of means to ensure timely access to such services would thus be important. Having a physician on site would not likely add additional interventional medical capabilities because of a lack of equipment and medications (e.g., electrocardiograph equipment).

3. The guidance's requirements, as currently stated, would have a chilling effect on the ability of a blood collection facility to mount mobile apheresis collection operations. The proposed alternative would allow continuation of these important efforts while ensuring donor safety.

Page 8, Information Provided to the Donor: The information required to be provided to the donor should be restricted to information necessary for a donor's informed consent; specifically, a schedule of donation types and interdonation intervals should not be required except to mention that such a schedule exists. (For example: "The kind of donation you give will determine how soon you can again donate. A staff person will be happy to tell you before you leave when you can donate again.")

1. Donors already have so much to read and answer that simplification of processes should be sought whenever possible to encourage donor comprehension.

2. The required interdonation intervals as stated in the draft guidance would lead to an inordinately complex and lengthy description for donors that will likely not be readily comprehendible (if it is even read!). Furthermore, at the time the donor is reading it, he/she may well not know whether a single, double or triple plateletpheresis will be (able to be) performed. Thus, the information will not be useful. Even with the simplification of the interdonation interval requirements as proposed above, the complexities of red cell loss and intercurrent whole blood donations will render any table or description useless for a donor.

Page 9, Process Validation: Additional information should be provided regarding the manner in which automated platelet counting instruments should be validated for the purpose of enumerating platelets in Platelets, Pheresis.

1. As is well known in the industry and to the agency, currently available automated instruments intended for counting platelets in whole blood samples of patients provide widely divergent platelet counts when applied to platelet-rich plasma from platelet components. A reference method for counting platelets has been published (*Am J Clin Pathol* 2001; 115:460-4), and an immunologically based method has been shown to compare accurately to this (*Br J Haematol* 2000;108:228-35). Blood collecting agencies should be required to validate their counting method against a reference technique such as one of these. Utilization of methods that have not been appropriately validated and calibrated leads to discrepancies in platelet content calculation and inappropriate decisions regarding patient dosing and determination of whether recipients of the units are refractory to platelet transfusion.

2. An alternative would be to publicize a listing of those hematology instruments that have been approved for counting platelets in platelet-rich plasma and require the use of one of these. (Such a requirement would parallel the requirement that only approved bacterial detection equipment be used and that it be used according to its package insert.) The list of approved instruments is a short one and one that is not widely known.

Page 11, Product Performance Qualification: This section requires clarifications regarding what to do with a performance failure during qualification and the method used for bacterial testing.

1. One failure in a qualifying test in 93 attempts is regarded as successful completion of the requirements, as I read this section. However, the guidance appears to direct that a single failure prior to the 93 attempts having been reached should cause a re-starting of the process. A second failure would certainly cause a re-start, but a single failure, followed by success throughout the other 92 attempts, should be regarded as a successful qualification attempt. The lone failure need not occur on test #93!

2. The requirement for 500 successful (sterile) bacterial cultures for qualification is at variance with the table on page 12 (which seems to require 99% sterility). Furthermore, the requirement of 500 successive sterile cultures is unlikely to be met given the usual means of culturing (outside a laminar flow hood), and the reported rate for false-positive cultures approximates or exceeds this value.

   In setting the required number of cultures, the agency should take into account the likely source of contamination. The donor's bloodstream is already acknowledged as a source that would not serve to disqualify the qualification process. The manufacturer of the collection set would have already submitted substantial evidence of successful sterilization processes, making this an unlikely source. Any "systemic" problem is most likely attributable to the phlebotomist's preparation of the venipuncture site, an issue unrelated to the apheresis itself. Therefore, the agency should carefully consider what it is trying to verify through this qualification process and not replicate requirements from the (now-ancient, open-system) past in the current era.

   Requirement of 99% sterility with 100% of units not being contaminated by the apheresis collection system (or device and disposables) seems reasonable. The number of collections to be required, however, should not exceed that required for the other parameters to be evaluated during the qualification process (i.e., 60 or 90 units).

Page 11, Product Performance Qualification: The timing of individual parameters should be specified rather than citing that a third should be tested early in storage, a third in mid-storage, and a third at the end of storage.

1. Leukocyte content should be determined within 24h of collection of the component in all cases for accuracy and a "worst-case" estimation.

2. pH should generally be determined at the end of the storage period, although the "one-third in each age range" approach offered in the draft guidance is reasonable given the current capabilities of storage containers.

Page 18, Component Testing: The appropriate specific gravity to be used should be stated in the document.

1. The agency is correct that a weight:volume correction (is, specific gravity factor) should be used when converting unit mass to unit volume.

2. Consistency of practice would be enhanced by the document stating what specific gravity should be used. A specific gravity of 1.05 g/mL is suggested.

Page 20, Acceptance Criteria (and elsewhere): The document appropriately notes the requirement of recovery of at least 85% of the platelet content of a unit after leukoreduction. This requirement should be clarified as pertaining to filtration methods of leukoreduction. The requirement is not applicable to apheresis procedures (e.g., Trima) that do not use filtration after collection to achieve leukoreduction.

Page 30, Scan Statistics: The required sample sizes for smaller collection facilities (i.e., those collecting fewer than 4,000 Platelets, Pheresis annually) should be specified through an enlarged table.

1. The use and details of scan statistics are a helpful inclusion in this document.

2. Many hospital-based blood collection establishments collect fewer than 4,000 Platelets, Pheresis annually; expanding the table to accommodate application of the approach to them would obviate the need to contact the agency.

3. If the agency leaves the table as it stands in the draft guidance, publication of a specific phone number for this contact for lower-volume facilities would be helpful.

Thank you for the opportunity to comment on this document.

Sincerely,

James P. AuBuchon, MD

Dartmouth Medical School • Dartmouth-Hitchcock Clinic • Mary Hitchcock Memorial Hospital • V.A. Medical Center, White River Junction, VT

One Medical Center Drive • Lebanon, NH 03756 • Tel: (603)650-5000 • www.dhmc.org